II. Non-Technical Abstract

There are presently more than 40,000 new cases of melanoma in the U.S. per year with 7,300 melanoma-related deaths. Patients with stage III disease have at least a 50% chance of recurrence after surgical resection; patients with stage IV melanoma have a median survival of less than 1 year and most of these patients eventually die of melanoma. Standard therapy is dacarbazine chemotherapy, and while response rates range from 8-25%, there is little evidence that treatment improves survival. Combination chemotherapy and biochemotherapy regimens have been reported to induce higher response rates with the disadvantage of greater toxicity and, to date, there is no evidence that they result in improved survival. New approaches to the treatment of this disease are needed.

The overall goal of this study is to develop ways to vaccinate against melanoma. In particular, we are trying to immunize against tyrosinase, which is the substance found in melanoma cells that helps to produce its black color. This study is designed to establish a safe and effective dose of two DNA vaccines for tyrosinase. The vaccine is a piece of DNA purified from bacteria which contains the gene for tyrosinase. DNA is the blueprint that cells use to produce the substances that make up the body. We are testing two types of DNA vaccines against tyrosinase. One vaccine is made from a piece of DNA that contains the blueprint for tyrosinase from humans and the other vaccine is made from DNA containing the code for tyrosinase from mice, which is very similar but not identical to human tyrosinase DNA. We do not know which is the best DNA vaccine to use. Patients will be assigned to a vaccine group on a random basis. We will first start vaccinating with either human or mouse tyrosinase DNA and then switch the vaccine to the other DNA after the third vaccination. We are comparing the ability of each of these vaccines to boost the immune response to tyrosinase on melanoma cells. We expect 18 patients to participate in this study.

The purpose of this study is to see if we can immunize against melanoma and to compare the two types of vaccine to see if one is better than the other. We will also study whether the vaccines cause any side effects. All of the patients on this study will receive vaccine, but groups of patients will receive increasing doses. Because of this, the first patients to be treated in this study will receive lower doses of the vaccine than the later patients, watching for side-effects to be sure that it is safe to give the higher doses. We believe, based on laboratory experiments, that the use of DNA vaccines could result in the production of immune substances (antibodies and T-cells) which recognize melanoma cells.

Patients will be treated in the outpatient Clinical Immunology unit and will receive vaccinations into the skin and into a muscle approximately every three weeks for the first 18 weeks of the study. The injections are given intramuscularly by a needleless device called a Bioject2000. This device is held in the hand and shoots the vaccine into the muscle. Blood will be drawn at regular intervals for analysis of antibodies

and T-cells. We will also be monitoring patients for any evidence of an effect on tumors.